In the Claims

The following list of claims will replace all prior versions and listings of claims in the Application. Please amend the claims as follows.

1. (currently amended) A mixture of conjugates each comprising a human growth hormone drug coupled to an oligomer that comprises a polyalkylene glycol moiety and a lipophilic moiety, said mixture having a molecular weight distribution with a standard deviation of less than about 22 Daltons.

2. (original) The mixture according to Claim 1, wherein the standard deviation of the molecular weight distribution is less than about 14 Daltons.

3. (original) The mixture according to Claim 1, wherein the standard deviation of the molecular weight distribution is less than about 11 Daltons.

4. (currently amended) The mixture according to Claim 1, wherein the polyalkylene glycol moiety has at least 2~~, 3 or 4~~ polyalkylene glycol subunits.

5. (currently amended) The mixture according to Claim 1, wherein the polyalkylene glycol moiety has at least 5 ~~or 6~~ polyalkylene glycol subunits.

6. (original) The mixture according to Claim 1, wherein the polyalkylene glycol moiety has at least 7 polyalkylene glycol subunits.

7. (currently amended) ~~The mixture according to Claim 6, wherein the polyalkylene glycol moiety is~~ A mixture of conjugates each comprising a growth hormone drug coupled to an oligomer that comprises a polypropylene glycol moiety having at least 7 polypropylene glycol subunits, said mixture having a molecular weight distribution with a standard deviation of less than about 22 Daltons.

8. (currently amended) The mixture according to Claim 7, wherein the polypropylene glycol moiety is uniform.

9. (cancelled)

10. (currently amended) The mixture according to Claim ~~9~~ 1, wherein the oligomer is covalently coupled to an amino function of the human growth hormone.

11. (original) The mixture according to Claim 10, wherein the amino function is at an amino acid residue of the human growth hormone selected from the group consisting of Phe^{1}, Lys^{38}, Lys^{41}, Lys^{70}, Lys^{115}, Lys^{140}, Lys^{145}, Lys^{158}, Lys^{168} and Lys^{172}.

12. (currently amended) The mixture according to Claim ~~9~~ 1, wherein the conjugate comprises a plurality of oligomers.

13. (currently amended) ~~The mixture according to Claim 1, wherein the~~ A mixture of conjugates each comprising a growth hormone drug coupled to an oligomer that comprises ~~polyalkylene glycol moiety is~~ a polypropylene glycol moiety, said mixture having a molecular weight distribution with a standard deviation of less than about 22 Daltons.

14. (original) The mixture according to Claim 13, wherein the polypropylene glycol moiety is uniform.

15. (currently amended) The mixture according to Claim ~~1~~ 13, wherein the oligomer consists of a uniform polypropylene glycol moiety and wherein the conjugates are each amphiphilically balanced such that each conjugate is aqueously soluble and able to penetrate biological membranes.

16. (currently amended) The mixture according to Claim 1, wherein the human growth hormone drug is covalently coupled to the oligomer.

17. (currently amended) The mixture according to Claim 16, wherein the human growth hormone drug is covalently coupled to the oligomer by a hydrolyzable bond.

18. (currently amended) The mixture according to Claim 1, wherein the human growth hormone drug is covalently coupled to the polyalkylene glycol moiety.

19. (currently amended) The mixture according to Claim 18, wherein the ~~oligomer further comprises a~~ lipophilic moiety is covalently coupled to the polyalkylene glycol moiety.

20. (cancelled)

21. (currently amended) The mixture according to Claim ~~20~~ 1, wherein the human growth hormone drug is covalently coupled to the lipophilic moiety.

22. (original) The mixture according to Claim 1, wherein the conjugate comprises a plurality of oligomers.

23. (original) The mixture according to Claim 22, wherein each oligomer in the plurality of oligomers is the same.

24. (currently amended) ~~The mixture according to Claim 1, wherein the oligomer comprises~~ A mixture of conjugates each comprising a growth hormone drug coupled to an oligomer that comprises a first polyalkylene glycol moiety covalently coupled to the growth hormone drug by a non-hydrolyzable bond and a second polyalkylene glycol moiety covalently coupled to the first polyalkylene glycol moiety by a hydrolyzable bond, said mixture having a molecular weight distribution with a standard deviation of less than about 22 Daltons.

25. (original) The mixture according to Claim 24, wherein the oligomer further comprises a lipophilic moiety covalently coupled to the second polyalkylene glycol moiety.

26. (original) The mixture according to Claim 1, wherein the conjugates are each amphiphilically balanced such that each conjugate is aqueously soluble and able to penetrate biological membranes.

27. (original) A pharmaceutical composition comprising:

the mixture according to Claim 1; and

a pharmaceutically acceptable carrier.

28. (currently amended) A method of treating human growth hormone deficiency in a subject in need of such treatment, said method comprising:

administering an effective amount of a mixture of conjugates, each comprising a human growth hormone drug coupled to an oligomer that comprises a polyalkylene glycol moiety and a lipophilic moiety, said mixture having a molecular weight distribution with a standard deviation of less than about 22 Daltons, to the ~~patient~~ subject to treat the human growth hormone deficiency.

29. (currently amended) A method of accelerating the growth rate of ~~an animal~~ a human subject, said method comprising:

administering to the ~~animal~~ human subject a mixture of conjugates each comprising a human growth hormone drug coupled to an oligomer that comprises a polyalkylene glycol moiety and a lipophilic moiety, said mixture having a molecular weight distribution with a standard deviation of less than about 22 Daltons, in an amount sufficient to accelerate the ~~animal's~~ human subject's growth rate.

30. (currently amended) A substantially monodispersed mixture of conjugates, each conjugate comprising a human growth hormone drug coupled to an oligomer that comprises a polyalkylene glycol moiety and a lipophilic moiety.

31. (currently amended) The mixture according to Claim 30, wherein the polyalkylene glycol moiety has at least 2~~, 3 or 4~~ polyalkylene glycol subunits.

32. (currently amended) The mixture according to Claim 30, wherein the polyalkylene glycol moiety has at least 5 ~~or 6~~ polyalkylene glycol subunits.

33. (currently amended) The mixture according to Claim 30, wherein the polyalkylene glycol moiety has at least 7 polyalkylene glycol subunits.

34. (currently amended) The mixture according to Claim 30, wherein at least about ~~96, 97, 98 or 99~~ percent of the conjugates in the mixture have the same molecular weight.

35. (original) The mixture according to Claim 30, wherein the mixture is a monodispersed mixture.

36. (original) The mixture according to Claim 30, wherein the mixture is a substantially purely monodispersed mixture.

37. (currently amended) The mixture according to Claim 30, wherein at least about ~~96, 97, 98 or 99~~ percent of the conjugates in the mixture have the same molecular weight and have the same molecular structure.

38. (original) The mixture according to Claim 30, wherein the mixture is a purely monodispersed mixture.

39. (currently amended) ~~The mixture according to Claim 30, wherein the polyalkylene glycol moiety is a~~ A substantially monodispersed mixture of conjugates, each conjugate comprising a growth hormone drug coupled to an oligomer that comprises a uniform polypropylene glycol moiety.

40. (currently amended) ~~A substantially monodispersed mixture of conjugates, each conjugate comprising human growth hormone covalently coupled to an oligomer that comprises a~~ The mixture according to Claim 39, wherein the uniform polypropylene glycol moiety ~~having~~ comprises at least 7 polypropylene glycol subunits.

41. (currently amended) The mixture according to Claim 40, wherein the ~~oligomer consists of a~~ uniform polypropylene glycol moiety ~~having~~ comprises at least 7 polypropylene glycol subunits, and wherein each conjugate is amphiphilically balanced such that each conjugate is aqueously soluble and able to penetrate biological membranes.

42. (currently amended) A mixture of conjugates each comprising a human growth hormone drug coupled to a polymer having a polyalkylene glycol moiety and a lipophilic moiety, wherein the mixture has a dispersity coefficient (DC) greater than 10,000 where

$$DC = \frac{\left(\sum_{i=1}^{n} N_i M_i\right)^2}{\sum_{i=1}^{n} N_i M_i^2 \sum_{i=1}^{n} N_i - \left(\sum_{i=1}^{n} N_i M_i\right)^2}$$

wherein:

n is the number of different molecules in the sample;

N_i is the number of i^{th} molecules in the sample; and

M_i is the mass of the i^{th} molecule.

43. (original) The mixture according to Claim 42, wherein the dispersity coefficient is greater than 100,000.

44. (original) The mixture according to Claim 42, wherein the dispersity coefficient is greater than 500,000.

45. (cancelled)

46. (currently amended) ~~The mixture according to Claim 42, wherein the polyalkylene glycol moiety is a~~ A mixture of conjugates each comprising a growth hormone drug coupled to a polymer having a polypropylene glycol moiety, wherein the mixture has a dispersity coefficient (DC) greater than 10,000 where

$$DC = \frac{\left(\sum_{i=1}^{n} N_i M_i\right)^2}{\sum_{i=1}^{n} N_i M_i^2 \sum_{i=1}^{n} N_i - \left(\sum_{i=1}^{n} N_i M_i\right)^2}$$

wherein:

n is the number of different molecules in the sample;

N_i is the number of i^{th} molecules in the sample; and

M_i is the mass of the i^{th} molecule.

47. (currently amended) The mixture according to Claim ~~42~~ 46, wherein the polypropylene glycol moiety is uniform.

48. (original) The mixture according to Claim 42, wherein the polyalkylene glycol moiety has at least 7 polyalkylene glycol subunits.

49. (currently amended) A mixture of conjugates in which each conjugate:

(a) comprises a human growth hormone drug coupled to an oligomer comprising a polyalkylene glycol and a lipophilic moiety; and

(b) has the same number of polyalkylene glycol subunits.

50. (cancelled)

51. (currently amended) ~~The mixture according to Claim 49, wherein the polyalkylene glycol moiety is a~~ A mixture of conjugates in which each conjugate

(a) comprises a growth hormone drug coupled to an oligomer comprising a polypropylene glycol moiety; and

(b) has the same number of polypropylene glycol subunits.

52. (original) The mixture according to Claim 51, wherein the polypropylene glycol moiety is uniform.

53. (original) The mixture according to Claim 49, wherein the polyalkylene glycol moiety has at least 7 polyalkylene glycol subunits.

54. (currently amended) A mixture of conjugates in which each conjugate has the same molecular weight and has the formula:

$$\text{Growth Hormone Drug}-\left[-B-L_h-G_i-R_m-G'_j-R'_n-G''_k-T\right]_p \qquad (A)$$

wherein:

B is a bonding moiety;

L is a linker moiety;

G, G' and G" are individually selected spacer moieties;

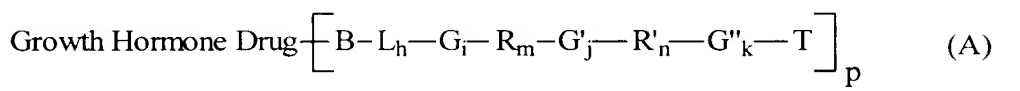
R is a lipophilic moiety and R' is a polyalkylene glycol moiety, or R' is the lipophilic moiety and R is the polyalkylene glycol moiety;

T is a terminating moiety;

h, i, j, k, m and n are individually 0 or 1, with the proviso that when R is the polyalkylene glycol moiety[;], m is 1[,]; and when R' is the polyalkylene glycol moiety, n is 1; and

p is an integer from 1 to the number of nucleophilic residues on the growth hormone drug.

55. (currently amended) ~~The mixture according to Claim 54, wherein the polyalkylene glycol group is a~~ A mixture of conjugates in which each conjugate has the same molecular weight and has the formula:



Growth Hormone Drug$-\left[B-L_h-G_i-R_m-G'_j-R'_n-G''_k-T\right]_p$ (A)

wherein:

B is a bonding moiety;

L is a linker moiety;

G, G' and G" are individually selected spacer moieties;

R is a lipophilic moiety and R' is a polypropylene glycol moiety, or R' is the lipophilic moiety and R is the polypropylene glycol moiety;

T is a terminating moiety;

h, i, j, k, m and n are individually 0 or 1, with the proviso that when R is the polypropylene glycol moiety, m is 1; and when R' is the polypropylene glycol moiety, n is 1; and

p is an integer from 1 to the number of nucleophilic residues on the growth hormone drug.

56. (original) The mixture according to Claim 55, wherein the polypropylene glycol group is uniform.

57. (original) The mixture according to Claim 54, wherein:

i, j, k, and n are 0;

R is uniform polypropylene glycol; and

the conjugates are each amphiphilically balanced such that each conjugate is aqueously soluble and able to penetrate biological membranes.

58. (original) The mixture according to Claim 54, wherein R is a polyalkylene glycol moiety having at least 7 polyalkylene glycol subunits.

59. (currently amended) A process for synthesizing a substantially monodispersed mixture of conjugates each conjugate comprising a growth hormone drug coupled to an oligomer that comprises a polyethylene glycol moiety, said process comprising:

reacting a substantially monodispersed mixture comprising compounds having the structure of Formula I:

$$R^1(OC_2H_4)_m\text{-}O^-X^+ \qquad (I)$$

wherein R^1 is H or a lipophilic moiety; m is from 1 to 25; and X^+ is a positive ion,

with a substantially monodispersed mixture comprising compounds having the structure of Formula II:

$$R^2(OC_2H_4)_n\text{-}OMs \qquad (II)$$

wherein R^2 is H or a lipophilic moiety; and n is from 1 to 25,

under conditions sufficient to provide a substantially monodispersed mixture comprising polymers having the structure of Formula III:

$$R^2(OC_2H_4)_{m+n}\text{-}OR^1 \qquad (III);$$

activating the substantially monodispersed mixture comprising polymers of Formula III to provide a substantially monodispersed mixture of activated polymers capable of reacting with a growth hormone drug; and

reacting the substantially monodispersed mixture of activated polymers with a ~~substantially monodispersed mixture of~~ growth hormone ~~drugs~~ drug under conditions sufficient to provide a substantially monodispersed mixture of conjugates each comprising a growth hormone drug coupled to an oligomer that comprises a polyethylene glycol moiety with m+n subunits.

60. (original) The process according to Claim 59, wherein R^2 is a fatty acid moiety or an ester of a fatty acid moiety.

61. (original) The process according to Claim 60, wherein the fatty acid moiety or the ester of a fatty acid moiety comprises an alkyl moiety at least 5 carbon atoms in length.

62. (original) The process according to Claim 59, wherein R^1 is a methyl group.

63. (original) The process according to Claim 59, further comprising:

reacting a substantially monodispersed mixture comprising compounds having the structure of Formula V:

$$R^2(OC_2H_4)_n\text{-}OH \qquad (V)$$

with a methanesulfonyl halide under conditions sufficient to provide a substantially monodispersed mixture comprising compounds having the structure of Formula II:

$$R^2(OC_2H_4)_n\text{-}OMs \qquad (II).$$

64. (original) The process according to Claim 63, further comprising:

reacting a substantially monodispersed mixture comprising compounds having the structure of Formula VI:

$$R^2\text{-}OMs \qquad (VI)$$

wherein R^2 is a lipophilic moiety;

with a substantially monodispersed mixture comprising compounds having the structure of Formula VII:

$$R^3(OC_2H_4)_m\text{-}O^-X_2^+ \qquad (VII)$$

wherein R^3 is benzyl, trityl, or THP; and X_2^+ is a positive ion;

under conditions sufficient to provide a substantially monodispersed mixture comprising compounds having the structure of Formula VIII:

$$R^3(OC_2H_4)_m\text{-}OR^2 \qquad (VIII); \text{ and}$$

reacting the substantially monodispersed mixture comprising compounds having the structure of Formula VIII under conditions sufficient to provide a substantially monodispersed mixture comprising compounds having the structure of Formula V:

$$R^2(OC_2H_4)_m\text{-}OH \qquad (V).$$

65. (original) The process according to Claim 59, further comprising:

reacting a substantially monodispersed mixture comprising compounds having the structure of Formula IV:

$$R^1(OC_2H_4)_n\text{-}OH \qquad (IV)$$

under conditions sufficient to provide a substantially monodispersed mixture comprising compounds having the structure of Formula I:

$$R^1(OC_2H_4)_n\text{-}O^-X^+ \qquad (I).$$

66. (original) The process according to Claim 59, wherein the activating of the substantially monodispersed mixture comprises reacting the substantially monodispersed mixture of polymers of Formula III with N-hydroxy succinimide to provide an activated polymer capable of reacting with a growth hormone drug.

67. (currently amended) The process according to Claim 59, wherein the growth hormone drug is human growth hormone, and wherein the reacting of the substantially monodispersed mixture of activated polymers with ~~a substantially monodispersed mixture of~~ human growth hormone comprises:

reacting the substantially monodispersed mixture of activated polymers with an amino function of an amino acid residue of the human growth hormone selected from the group consisting of Phe^1, Lys^{38}, Lys^{41}, Lys^{70}, Lys^{115}, Lys^{140}, Lys^{145}, Lys^{158}, Lys^{168}, Lys^{172} and combinations thereof to provide a substantially monodispersed mixture of conjugates each comprising a human growth hormone coupled to one or more oligomers that each comprise a polyethylene glycol moiety with m+n subunits.

68. (new) The mixture of claim 1, wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated alkyl moieties having 1 to 28 carbon atoms.

69. (new) The mixture of claim 1, wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated alkyl moieties having 2 to 12 carbon atoms.

70. (new) The mixture of claim 1, wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated natural fatty acid moieties having 2 to 18 carbon atoms.

71. (new) The mixture of claim 1 wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated natural fatty acid moieties having 3 to 14 carbon atoms.

72. (new) The mixture of claim 1, wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated natural fatty acid moieties having 4, 5 or 6 carbon atoms.

73. (new) The method of claim 28, wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated alkyl moieties having 1 to 28 carbon atoms.

74. (new) The method of claim 28 wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated alkyl moieties having 2 to 12 carbon atoms.

75. (new) The method of claim 28 wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated natural fatty acid moieties having 2 to 18 carbon atoms.

76. (new) The method of claim 28 wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated natural fatty acid moieties having 3 to 14 carbon atoms.

77. (new) The method of claim 28, wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated natural fatty acid moieties having 4, 5 or 6 carbon atoms.

78. (new) The method of claim 29 wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated alkyl moieties having 1 to 28 carbon atoms.

79. (new) The method of claim 29 wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated alkyl moieties having 2 to 12 carbon atoms.

80. (new) The method of claim 29 wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated natural fatty acid moieties having 2 to 18 carbon atoms.

81. (new) The method of claim 29 wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated natural fatty acid moieties having 3 to 14 carbon atoms.

82. (new) The method of claim 29 wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated natural fatty acid moieties having 4, 5 or 6 carbon atoms.

83. (new) The mixture of claim 30 wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated alkyl moieties having 1 to 28 carbon atoms.

84. (new) The mixture of claim 30 wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated alkyl moieties having 2 to 12 carbon atoms.

85. (new) The mixture of claim 30 wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated natural fatty acid moieties having 2 to 18 carbon atoms.

86. (new) The mixture of claim 30 wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated natural fatty acid moieties having 3 to 14 carbon atoms.

87. (new) The mixture of claim 30 wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated natural fatty acid moieties having 4, 5 or 6 carbon atoms.

88. (new) The mixture of claim 40 wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated alkyl moieties having 1 to 28 carbon atoms.

89. (new) The mixture of claim 40 wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated alkyl moieties having 2 to 12 carbon atoms.

90. (new) The mixture of claim 40 wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated natural fatty acid moieties having 2 to 18 carbon atoms.

91. (new) The mixture of claim 40 wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated natural fatty acid moieties having 3 to 14 carbon atoms.

92. (new) The mixture of claim 40 wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated natural fatty acid moieties having 4, 5 or 6 carbon atoms.

93. (new) The mixture of claim 42 wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated alkyl moieties having 1 to 28 carbon atoms.

94. (new) The mixture of claim 42 wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated alkyl moieties having 2 to 12 carbon atoms.

95. (new) The mixture of claim 42 wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated natural fatty acid moieties having 2 to 18 carbon atoms.

96. (new) The mixture of claim 42 wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated natural fatty acid moieties having 3 to 14 carbon atoms.

97. (new) The mixture of claim 49 wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated natural fatty acid moieties having 4, 5 or 6 carbon atoms.

98. (new) The mixture of claim 49 wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated alkyl moieties having 1 to 28 carbon atoms.

99. (new) The mixture of claim 49 wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated alkyl moieties having 2 to 12 carbon atoms.

100. (new) The mixture of claim 49 wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated natural fatty acid moieties having 2 to 18 carbon atoms.

101. (new) The mixture of claim 49 wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated natural fatty acid moieties having 3 to 14 carbon atoms.

102. (new) The mixture of claim 49 wherein the lipophilic moiety comprises one or more linear, saturated or unsaturated natural fatty acid moieties having 4, 5 or 6 carbon atoms.